TRANSCEND

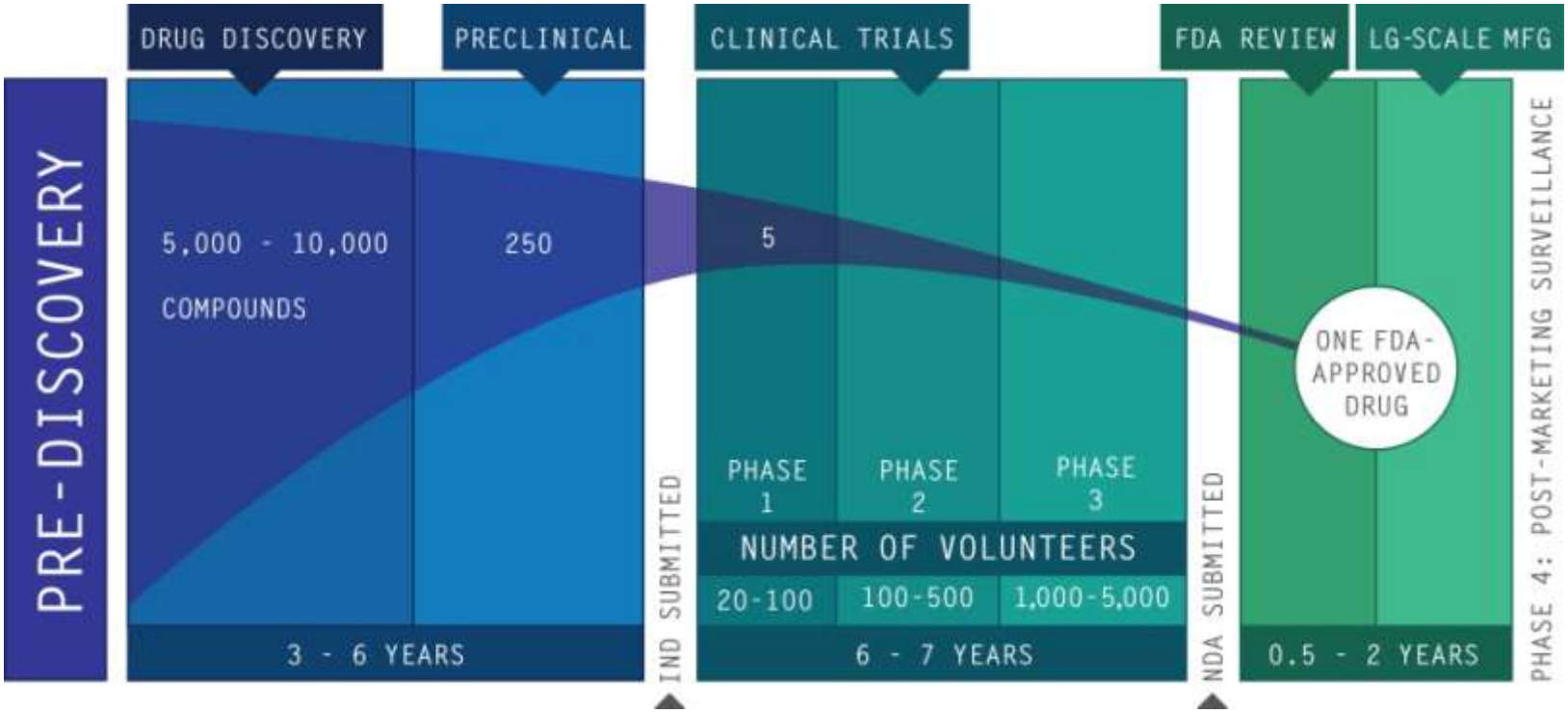
An IT Bundle to Support Adaptive Trials with Novel Agents and Emerging Biomarkers

Current Capabilities, Future Directions

June 22 , 2010

Laura Esserman, MD, MBA

Drug Development – Current Model



One FDA-Approved Drug - Start to Finish

- 10- 15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

It Is Time to Implement a More Efficient Clinical Trial Process

Inefficient clinical trials account for a majority of the time and cost associated with the failures of the current system

- Reduce time to conclusive results/Accelerate learning
- Reduce patients/volunteers required
- Reduce cost of conducting trials
- Increase collaboration/Data sharing

The Challenge in Breast Cancer

- Breast Cancer is a common and serious disease
- Screening is prevalent
  - Has increased the fraction of low risk tumors but only minimally decreased the fraction of high risk tumors
  - Denominator of many adjuvant trials includes lower risk tumors
- Many treatments have been successful in improving outcomes
  - But for women with aggressive cancers that do not respond well to current treatments, their prospect for survival is grim

I SPY 2: Designed to Optimize Success of Phase 3 Trials

Principle	Solution
Test agents where they matter most	•Neoadjuvant setting, poor prognosis cancers •Integrate advocates into trial planning
Rapidly learn to tailor agents	•Adaptive Design •Neoadjuvant therapy •Integration of biomarkers, imaging
Optimize Phase 3 trials	•Graduate drugs with predicted probability of success in Phase 3 trials for given biomarker profile
Drive Organizational Efficiency	•Adaptive Design •Master IND •Test drugs by class, across many companies •Shared cost of profiling •Financial support separated from drug supply •Shared IT Infrastructure, caBIG
Use Team Approach	•Democratize access to data •Share credit and opportunity •Collaborative process for development

Building on I-SPY 1

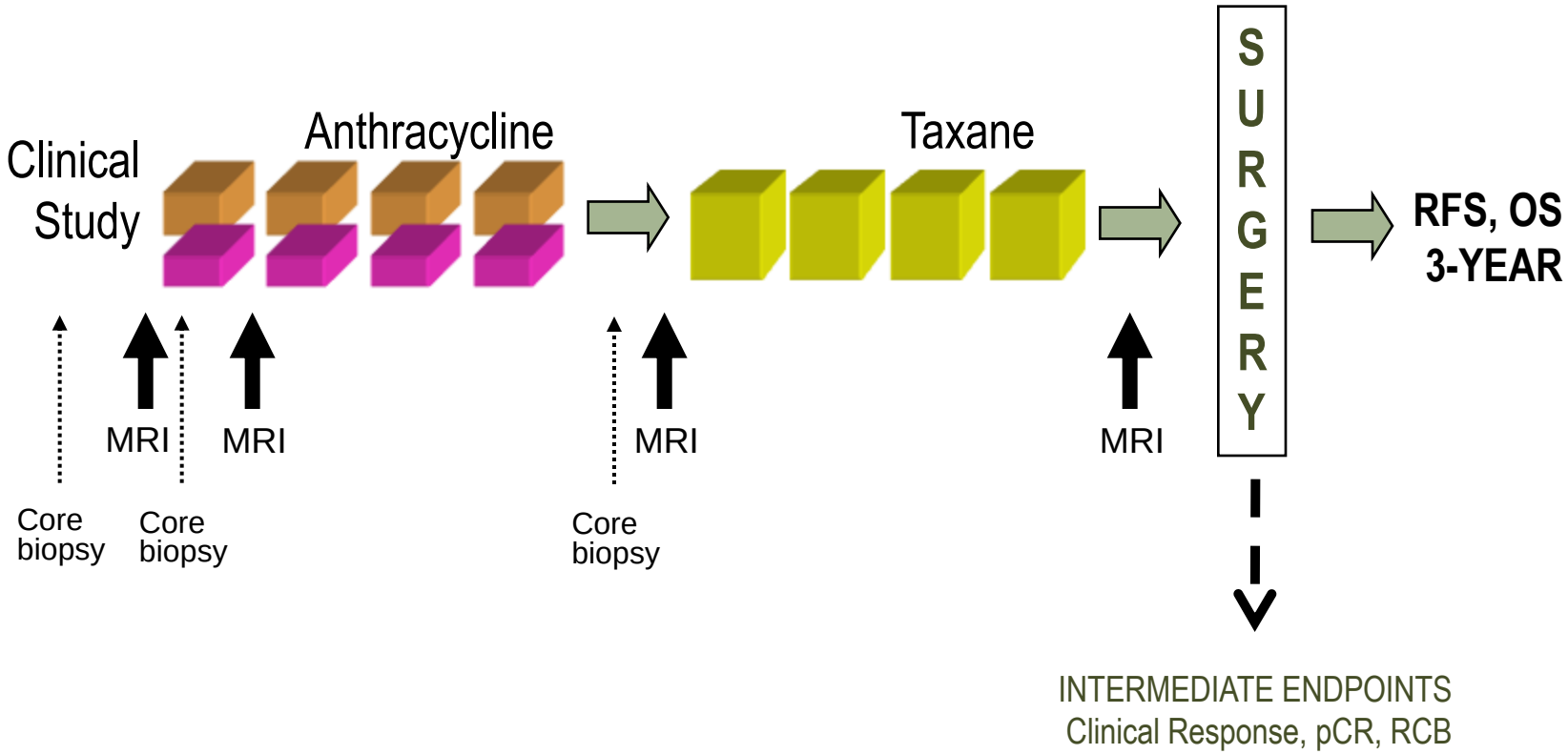
CALGB INTERSPORE ACRIN NCICB

CALGB 150012/150007 and ACRIN 6657

Investigation of
Serial studies to
Predict
Your
Therapeutic
Response with
Imaging and Molecular
Ana-
Lysis

I SPY WITH MY LITTLE EYE ...
A BIO-MARKER BEGINING WITH X...

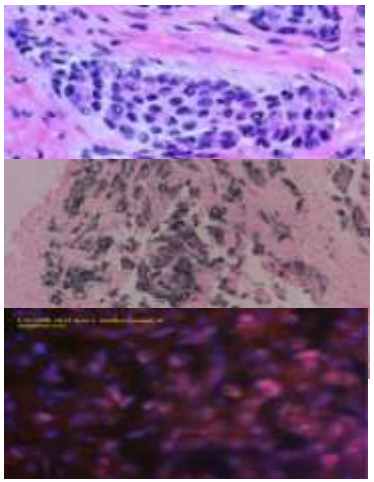
I-SPY 1/ACRIN 6657



I-SPY 1 Biomarker Platforms

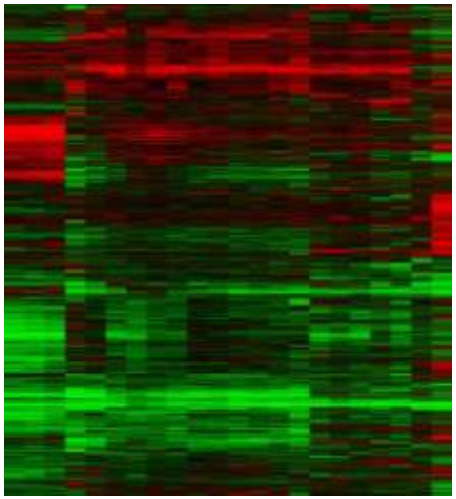
Tissue: Core or Surgical

H&E, IHC, FISH



UNC, Penn

Expression Arrays

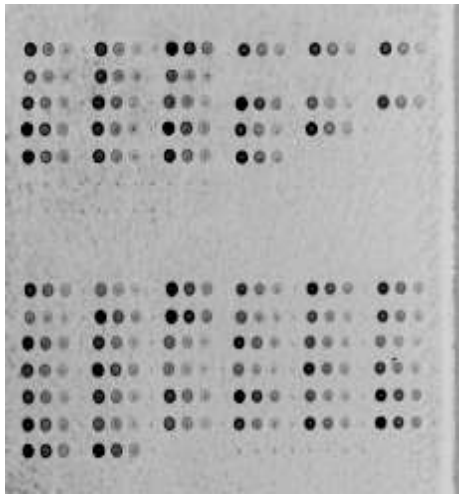


UNC, UCSF, NKI

p53 GeneChip

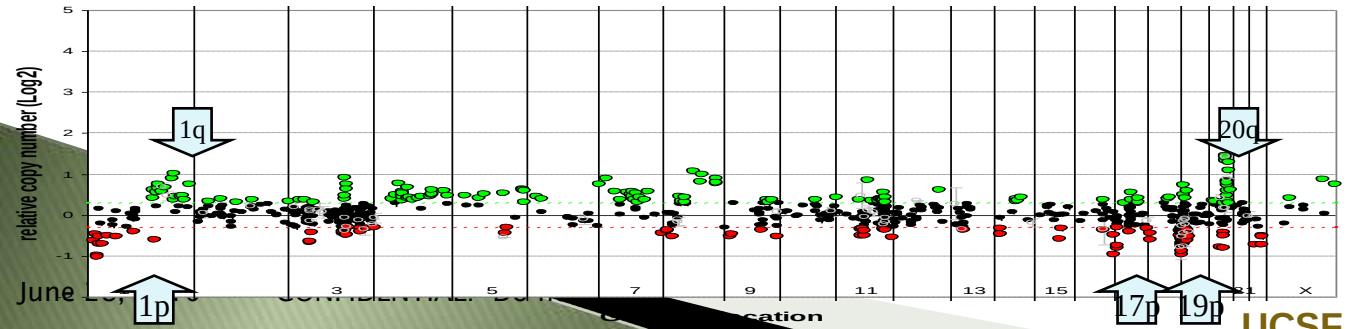
UNC

Protein Arrays (RPMA)



GMU

CGH

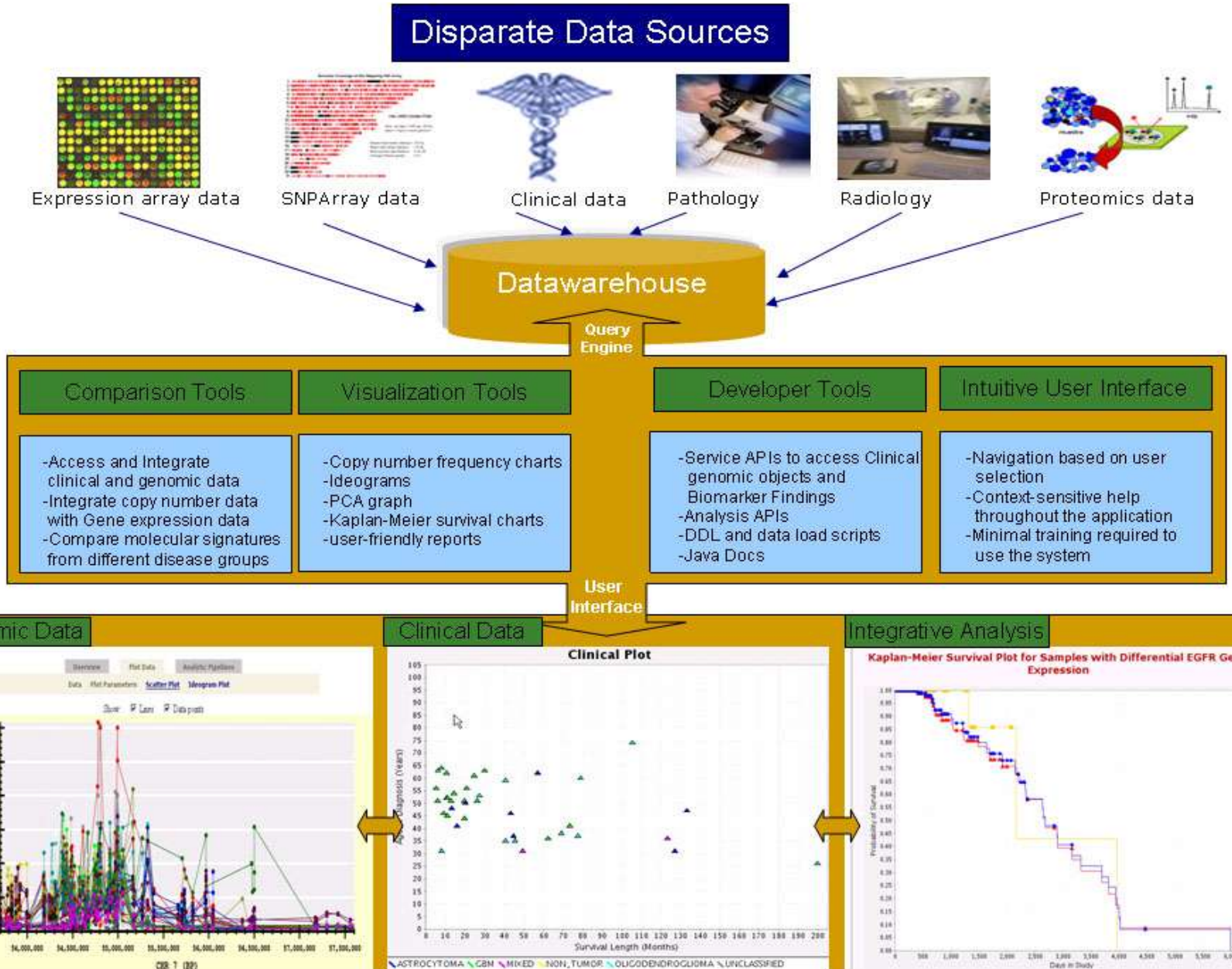


UCSF

Serum

Id1 proteins
autoantibodies
phospho proteins

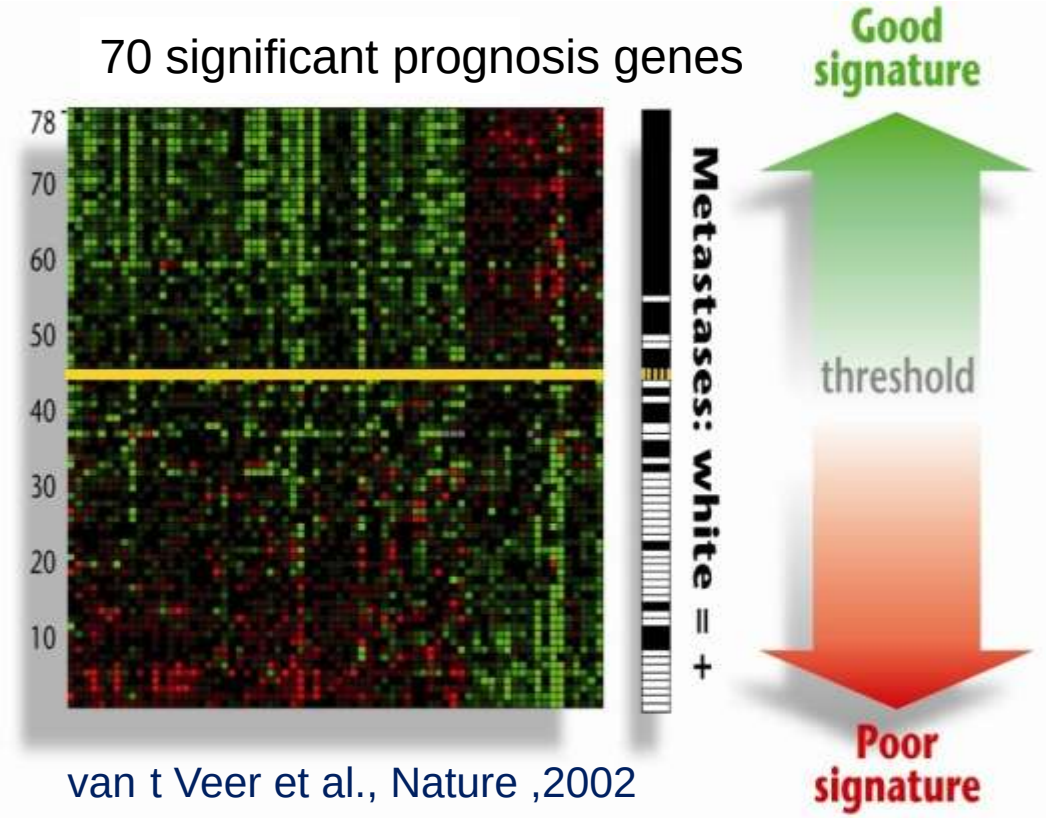
NCICB Infrastructure: caINTEGRATOR



I-SPY : Poor Prognosis Tumors

NKI 70 Gene Profile	
"Good" Signature	9%
"Poor" Signature	91%

Mean Tumor Size= 6.0
Present as clinical mass
55% < Age 50



van t Veer et al., Nature ,2002

Observations from I-SPY 1

- Patients in I-SPY are the very patients most at risk
  - 91% of I-SPY patients had poor risk biology
  - Therapies save lives in the adjuvant but not metastatic setting
- pCR (and RCB) are highly predictive of outcome
  - Stronger predictor when analyzed by subgroup (Simpson's paradox)
  - Can be used as a trial endpoint for evaluation of novel agents
- MRI Volume change is a non-invasive way to predict pCR and RCB 0,1

I-SPY 2 is Designed to

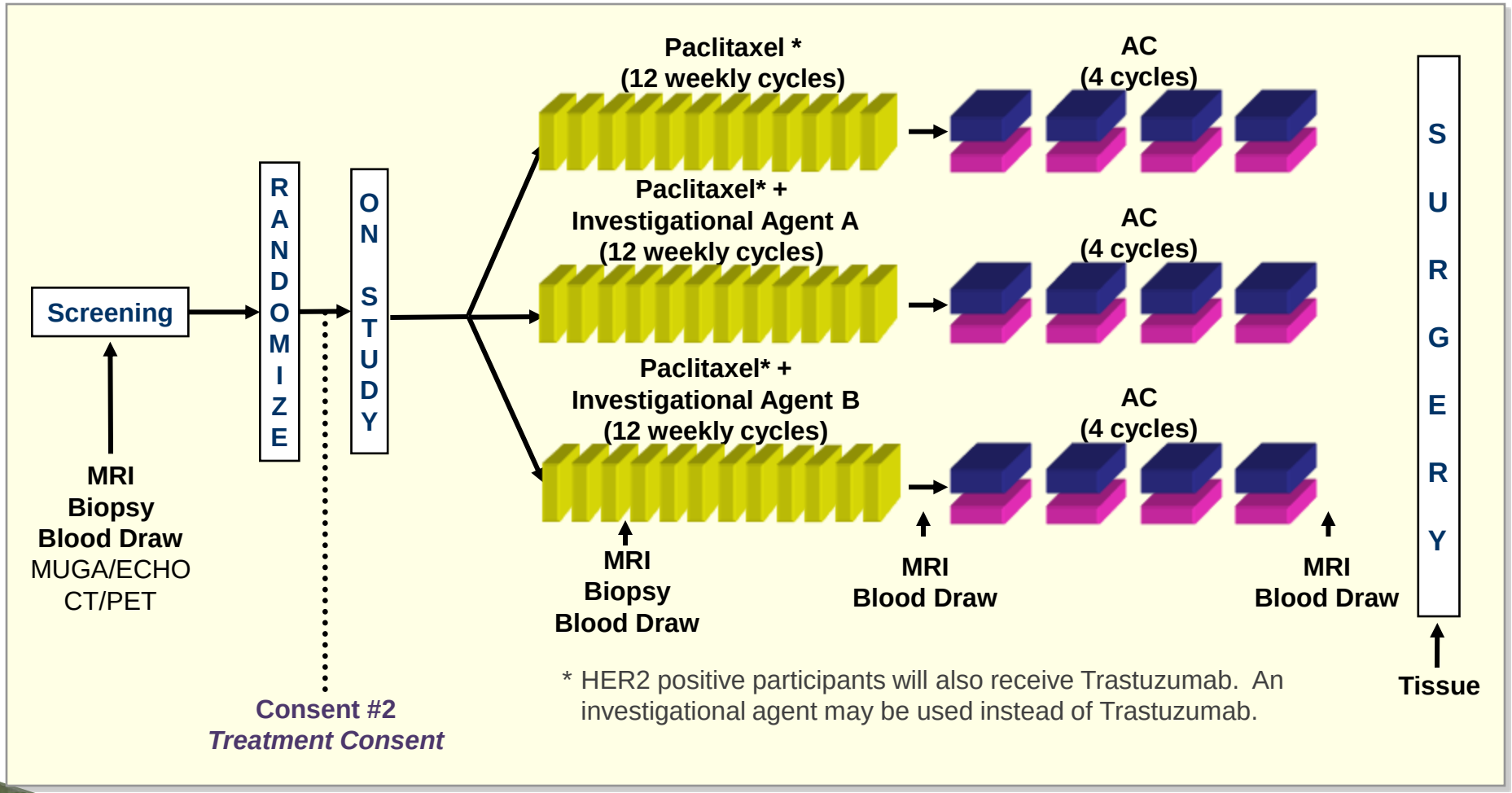
- Screen phase 2 agents in combination with standard chemotherapy in neoadjuvant setting
  - Endpoint is pCR
  - "threshold" is 85% predicted likelihood of success in a 300-patient phase 3 trial for drug biomarker pair
- Accelerate process of identifying drugs that are effective for specific breast cancer subtypes
  - Integration of biomarkers
- Reduce the cost, time, and numbers of patients needed to get effective drugs to market

Infrastructure of I-SPY 1→2

- Drive standards for
  - Data collection
  - Tissue Acquisition
  - Biomarker Assays
  - Imaging Acquisition (MRI)

- Culture of sharing
  - Data
  - Credit
  - Database that grows as investigators join
    - Regardless of who does the assay

I-SPY 2 Adaptive Trial Design



Biomarkers in I-SPY 2

- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established/Approved Biomarkers
  - IDE Biomarkers
  - Qualifying Biomarkers
  - Exploratory Biomarkers (discovery of new markers of response prediction)

FDA Cleared or Approved

CLIA

I-SPY 2 Adaptive Trial Schema: Screening & Randomization

Eligibility Assessment Process

Patient presents with newly diagnosed ≥ 2.5cm invasive tumor

Core biopsy to assess eligibility

Eligibility determined by:
- Ability to tolerate MRI
- Ability to generate 44k Agilent microarray

Is patient:
- **MammaPrint Low**
- ER + and HER2 –

No

Patient On Study
Randomized to treatment arm based on:
- ER, PR status
- HER2 Status
- MammaPrint score

Yes

Patient not on study
Not considered good candidate for chemotherapy

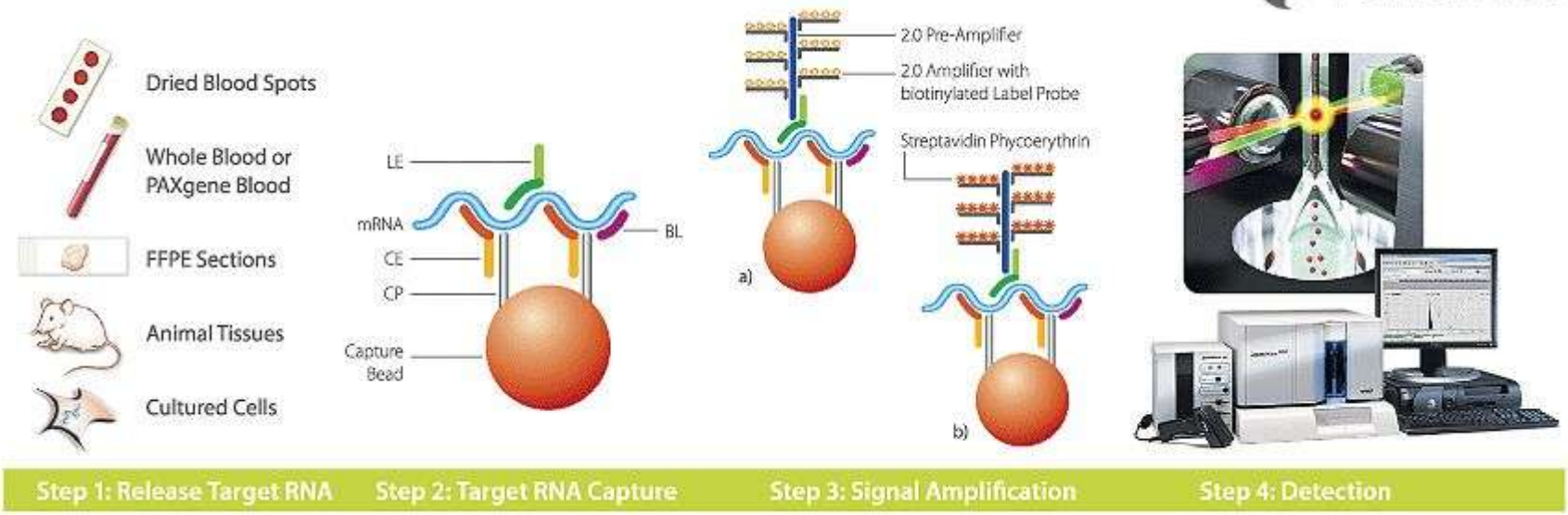
Qualifying Biomarker

Lawrence Berkeley National Lab 60 Cell Line Analysis using the Panomics QuantiGene Plex 2.0 Assay

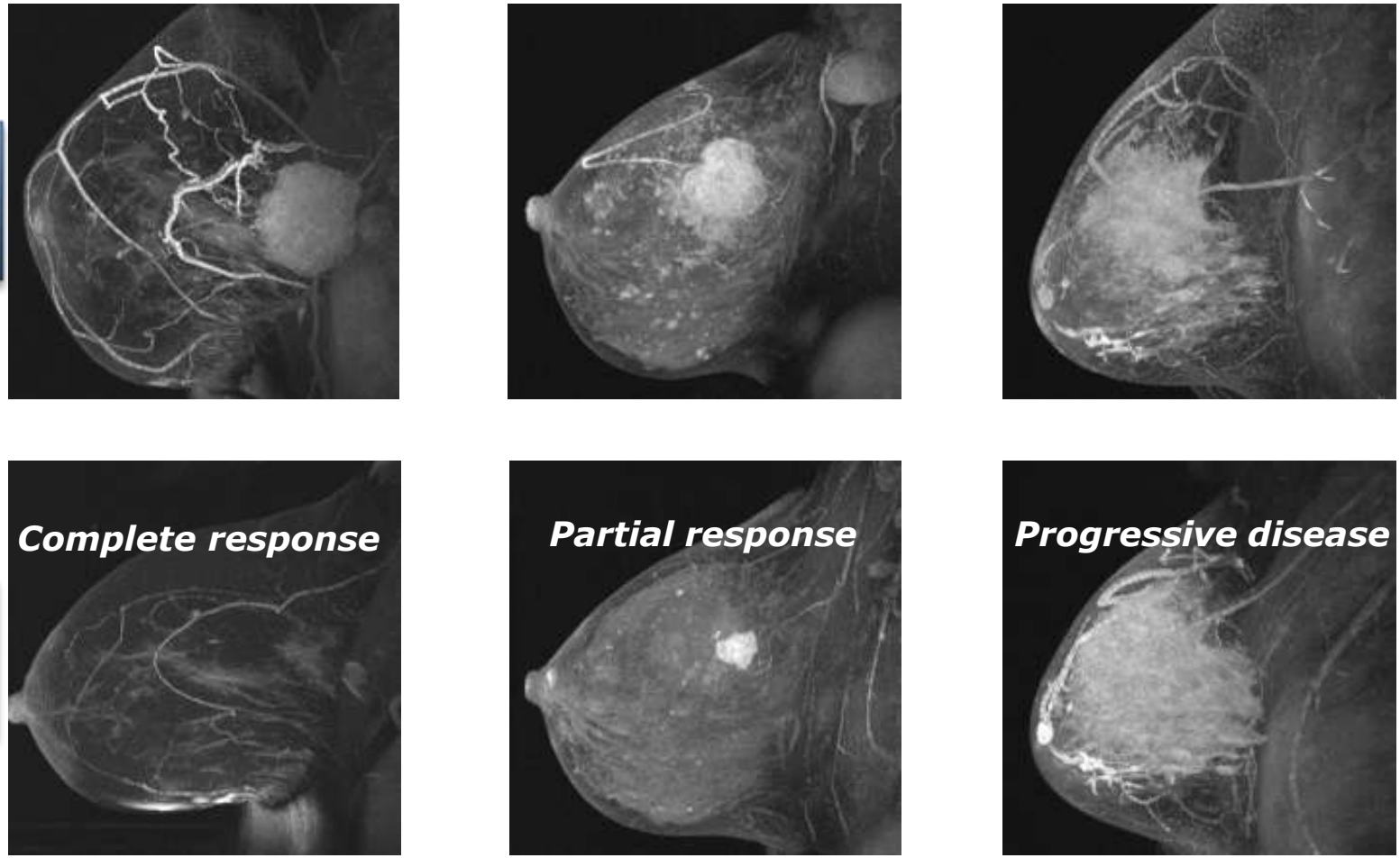
The participant's tumor is matched to one of the 60 cell lines using the gene expression profile determined using the Panomics QuantiGene Plex 2.0 Assay.

Panomics QuantiGene Plex 2.0 Assay Work Flow

Panomics



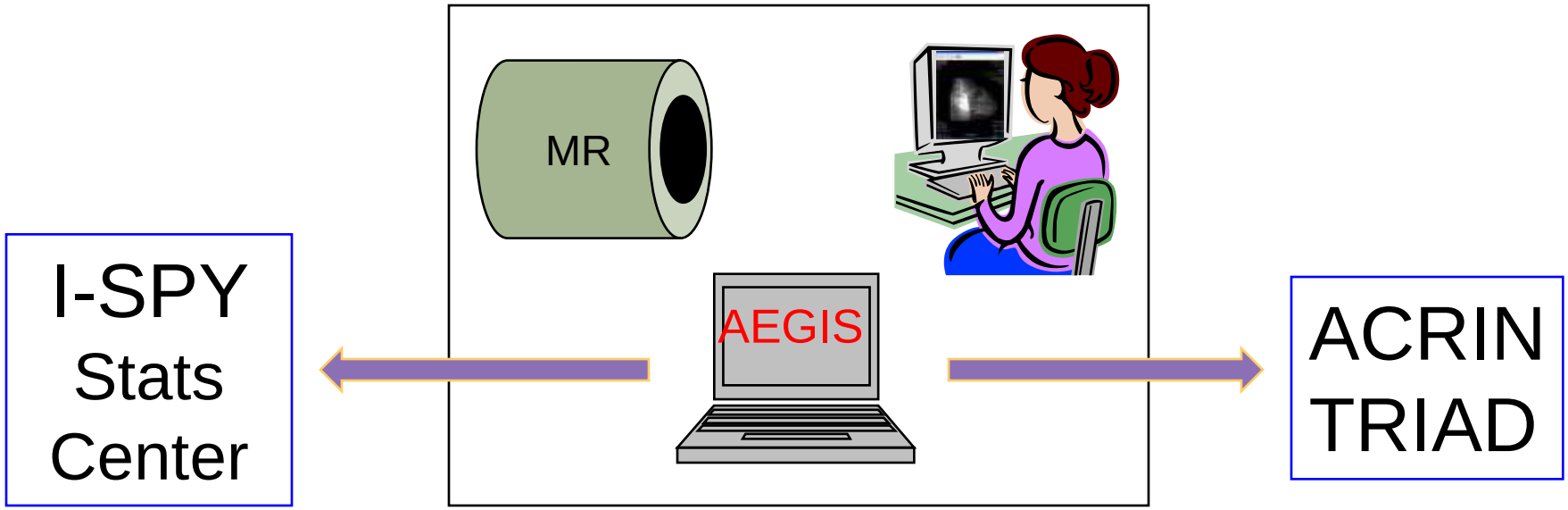
Imaging Biomarkers Provide Functional Markers of Response, Volume Reduction over Time



Nola Hylton, PhD

Radiology and Biomedical Imaging, UCSF

SER Volumetric Analysis in I-SPY 2



- Sentinelle Aegis workstations provided to all ISPY-2 sites
- Image data transfer from scanner to Aegis immediately following patient exam
- Volume computation performed by technologist or RA
- Radiologist confirmation obtained
- Image Data sent to ACRIN TRIAD
- Numerical volume data sent to ISPY Statistical Center

Advantages of Adaptive Design

- If the drug works better or worse than you think, you will learn that as the trial progresses
- Drugs can be dropped quickly if they are ineffective or harmful, or graduated sooner if they are clearly beneficial
- The trial will enable us to learn for each drug, which biomarker group or groups are optimal
- Trials can be smaller(usually), conclusions more accurate, treatment of patients in the trial better

Master IND Accommodates Testing of Multiple agents

- Eliminates need for new protocol each time an agent is added
- Enables approval as soon as an agent is “Tier 1” ready
- Provides pharmaceutical companies a pathway for rapid development, testing of promising agents
- Provides FDA with opportunity to test more efficient process of drug qualification
- Master IND to be held by FNIH

I-SPY 2 Adaptive Trial: Introduce several new agents for a given profile

Patient is on Study

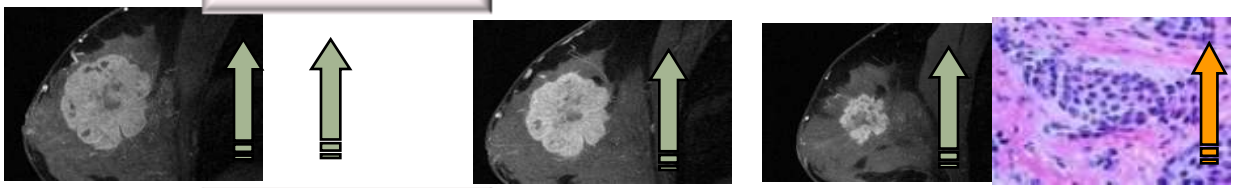
HER 2 (+)

Randomize

- Taxol + Trastuzumab
- Taxol + Trastuzumab* + New Agent A
- Taxol + Trastuzumab* + New Agent B
- Taxol + Trastuzumab* + New Agent C

AC → Surgery

Learn, Adapt from each patient as we go along



HER 2 (–)

Randomize

- Taxol
- Taxol + New Agent C
- Taxol + New Agent D
- Taxol + New Agent E

AC → Surgery

**Key*

MRI

Residual Disease (Pathology)

**Or equivalent*

I-SPY 2 Adaptive Trial: Learn, Drop, Graduate, and Replace Agents Over Time

Patient is on Study

HER 2 (+)

Randomize

- Taxol + Trastuzumab
- Taxol + Trastuzumab* + New Agent A
- Taxol + Trastuzumab* + New Agent B
- Taxol + Trastuzumab* + New Agent F

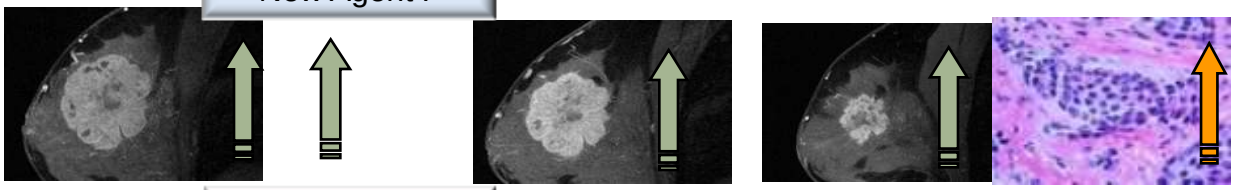
HER 2 (–)

Randomize

- Taxol
- Taxol + New Agent F
- Taxol + New Agent GH
- Taxol + New Agent E

AC → Surgery

Learn, Adapt from each patient as we go along



*Or equivalent

Key

MRI

Residual Disease (Pathology)

Being "adaptive" in trials
requires technology to be "adaptive"

- An iterative approach to evaluating therapeutic interventions/agents
- Adaptive functional requirements
  - Study participants can be excluded from arms based on biological characterization of their tumors
  - Arms (ie, agents) added/removed throughout the trial – a "running trial"
  - Outcome "measures" can be modified as technology advances – leverage new biomarker assays as they are validated and become available

TRANSCEND

TRANslational Informatics **S**ystem to **C**oordinate **E**merging Biomarkers, **N**ovel Agents, and Clinical **D**ata

Tolven™ Healthcare Innovations

caBIG™ Cancer Biomedical Informatics Grid™

TRANSCEND Objectives

- Develop an information management infrastructure to support adaptive clinical trials like I-SPY 2
- Demonstrate integration of a clinical system (electronic health record system) with a clinical research infrastructure
- Provide a demonstration of caBIG infrastructure in use in a large multi-center trial
- Support patient-centric interactions (patient calendar)

"Standard" Process is Inefficient

Standard

Clinician evaluates pt, records data

↓

Study Coordinator fills out CRF

↓

Coordinator faxes form to CALGB

↓

CALGB staff puts data into data base

↓

CALGB cleans data

↓

CALGB sends data to NCI

↓

Errors identified, study coordinators contacted

↓

Data sent back to CALGB

↓

Data re-cleaned and sent back to NCI

TRANSCEND

Clinician evaluates pt, uses web based structured tools to capture data

↓

CRF populated

↓

Biopsies acquired, caTISSUE populated

↓

Coordinator completes missing fields

↓

Quality, cleaning by DCC (24 hrs)

↓

Data submitted to randomization engine

↓

Anonymized data, including biomarker data, populates caINTEGRATOR

Informatics Aspects of I-SPY 2

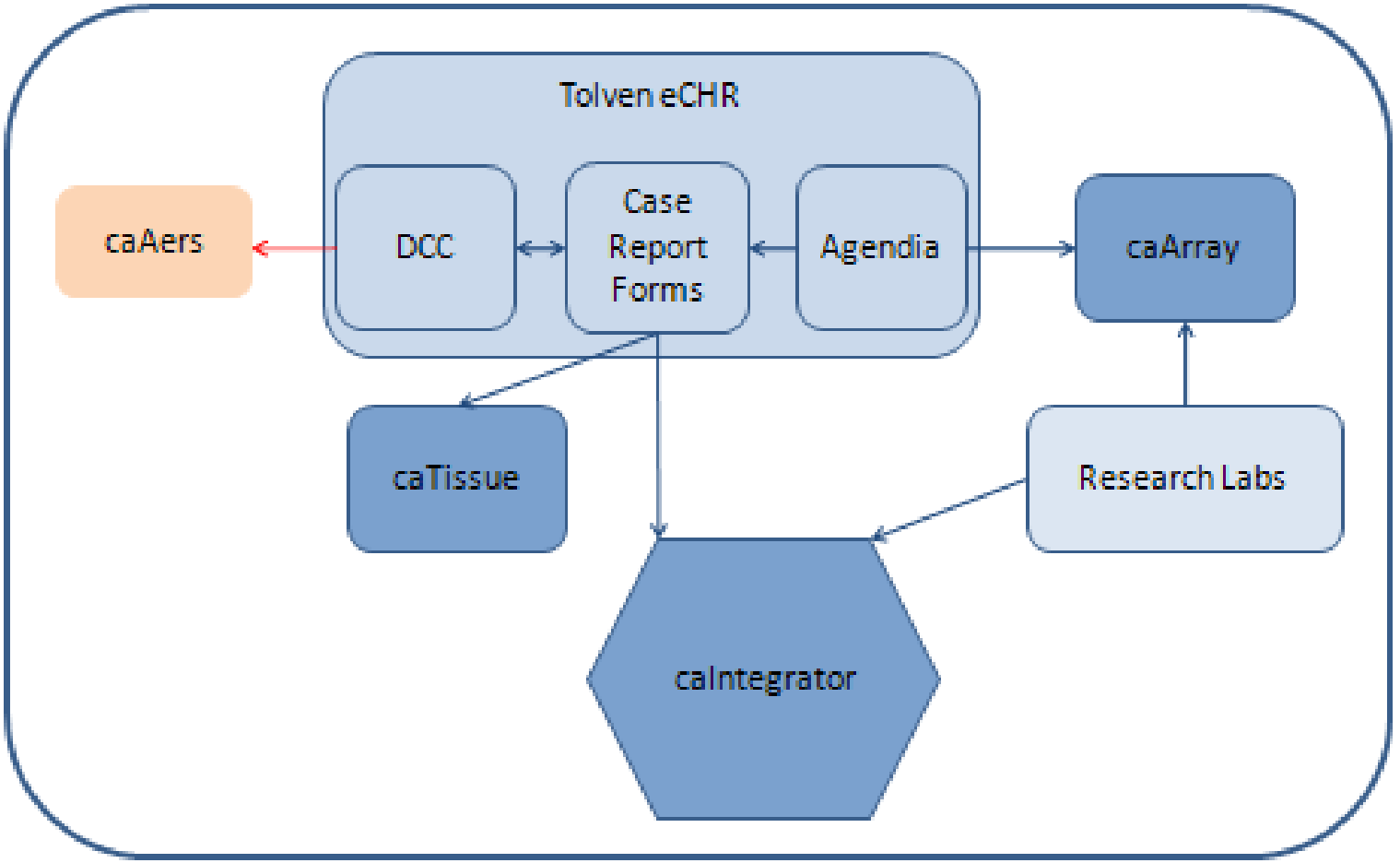
- Manage information across multiple sites
  - Single enterprise, not “multiple sites”
  - Adaptive randomization
- Facilitate fast, accurate information capture
  - Real time data cleaning as trial depends on rapid eligibility determination and randomization influenced by imaging response
- Combine evaluation of drugs and biomarkers
- Accommodate multiple biomarker types
  - arrays, imaging volume, numeric scales, etc.
- Provide portal for access to data early and in an integrated fashion (one stop shopping)
- Automate randomization as a web service (with review)

Components and Functionality in TRANSCEND v1.0

Functional Requirements	Components
Manages the patient registration lifecycle and eligibility determination	Tolven
Randomizes patients	MDACC Randomization Service
Tracks study participants	Tolven
Manages biological specimens	caTISSUE
Captures clinical data at the point of care and render CRFs using automated methods	Tolven
Provides traditional web-based CRFs	Tolven
Initiates the adverse event lifecycle	Tolven
Provides storage and retrieval of trial data for scientists	caINTEGRATOR; caARRAY

TRANSCEND Systems Overview

TRANSCEND



What TRANSCEND Looks Like

Patient visits the Physician

Clinical Information System (Tolven eCHR)

Eligibility is verified, patient is registered , clinical data is captured, tracks the patient schedule, identifies labs and allows them to be viewed/resulted

Randomization Service

Patients randomized to novel treatment arm

Biopecimen Data Management System (caTISSUE)

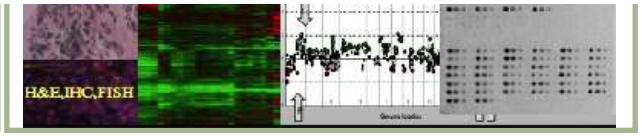
biospecimens are tracked

caINTEGRATOR

Microarray Data Storage (caARRAY)

Raw and normalized array data is stored

Qualifying & Exploratory Biomarkers



Investigators evaluate efficacy of treatment arms – as trial is underway

What is new or different about TRANSCEND?

- Randomization web service
- Using a clinical information system rather than Clinical Trials Management System to collect patient data for CRFs
- Integration of caTISSUE with a clinical information system in the context of a trial
- Using caINTEGRATOR v2.0 as a scientist portal to study data

TRANSCEND Design Lessons

- The clearer the requirements, the more likely to get what you intend
- Involve actual users in user interface design and workflow reviews
- Screen and report mock-ups are invaluable!
- Integrating with clinical systems demands an enterprise approach to information exchange (caXchange, HL-7)
- Move towards ‘enterprise bus’ as an integration rather than API-based point-to-point integration
- Install systems early to deal with logistical issues far in advance of needing the systems
- Do not underestimate the number of data elements you might want or need to code
- Identifying and managing data elements is a significant undertaking

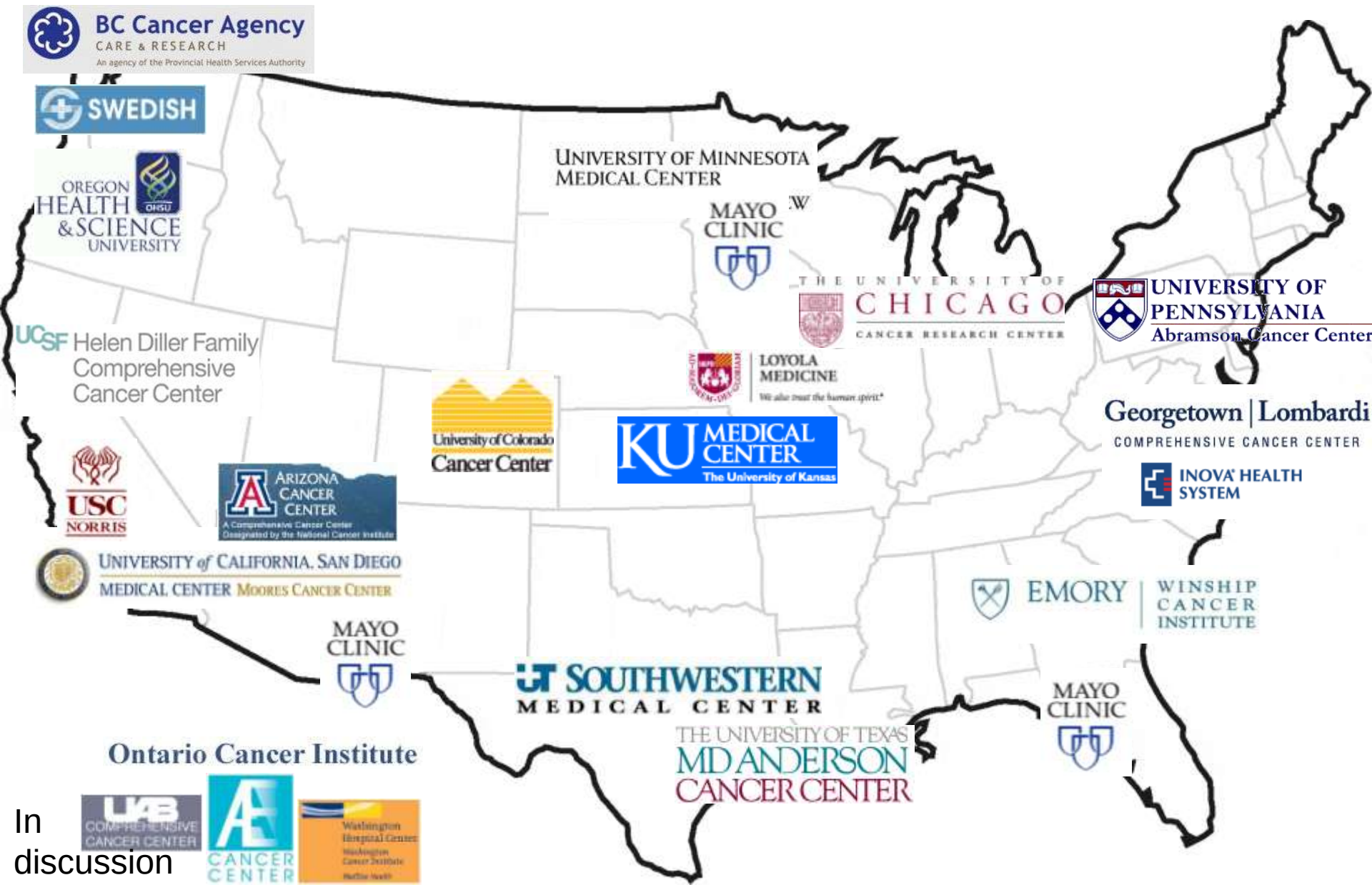
To TRANSCEND(2) Proposed Enhancements

- **Patient Communication and Care Plan**

- **Automated Data Safety Monitoring Board (DSMB) Adverse Event reporting**
  - Ability to capture expected toxicity curves by drug
  - Ability to trigger automated alerts to DSMB based on exceeding pre-defined toxicity thresholds and expected and unexpected adverse events

- **Interface allowing patients to directly input:**
  - Adherence to treatment regimens
  - Adverse events (MSKCC system→caAers)
  - Follow-up information

Projected I-SPY 2 study sites



In discussion

Drug Development – Accelerating Pace of Learning

SEAMLESSLY ENABLED BY THE INTEGRATION OF INFORMATION

AT THE POINT OF CARE
Biomarkers and Drugs by Class
To Adaptively Randomize in Trials
To Adaptively Learn in Practice

Compress Timeline for identifying effective drugs
Reduce time from phase 1→3
Reduce cost, # pts by 10-50 fold

Team Approach

To TRANSCEND(2) Proposed Enhancements

- **Automated sharing of clinical summary with trial site's Electronic Medical Record (EMR) systems**
  - TRANSCEND Administrative Capabilities
  - Ability to add and remove randomization arms and associated information including:
    - Investigational agent eligibility criteria and related tests
    - Expected adverse events
- **Quality Control for Biopspecimens, Biomarkers: caTISSUE Extensions**

Working Group Chairs

Data, Design	Don Berry
Imaging	Nola Hylton
Biomarkers	Laura Van't Veer
Operations	Angie DeMichele
Agent Selection	Doug Yee
Informatics	Mike Hogarth
Pathology	Fraser Symmans
Advocates	Jane Perlmutter
Project Management	Meredith Buxton, Donya Bagheri
NCI leadership:	Anne Barker, Gary Kelloff
FDA, CDER Leadership	Janet Woodcock, Karen Weiss
FNIH Leadership	David Wholley, Sonia Pearson-White
Pharma, Biotech	Bob Mass, David Chang, Gary Gordon, Chris Coughlin, Jose Barueca, Cameron , Antonio Gualberto, Alan Carter, Bernhard Sixt

TRANSCEND TEAM

- Meg Young – TRANSCEND Project Manager (UCSF)
- Sarah Davis – I-SPY 2 UCSF Trial Manager (UCSF)
  - Joyce Lee, Julia Lyanders (software testing, quality control)
- Sorena Nadaf – Informatics/Design (UCSF)
- Dr. Angela DeMichele – Clinical Oncology (U Penn)
- Kyle Walthen – Randomization Engine (MDA)
- Ashwin Koleth – Software Development (Tolven)
- John Koisch – Architecture (NCI)
- Kathy Hajopoulos – Project Oversight (UCSF)
- John Churin- Software lead engineer (Tolven)
- Nancy Roche – Project Oversight (SAIC)
- Dr. Laura Esserman –I-SPY TRIAL, TRANSCEND PI (UCSF)
- Dr. Michael Hogarth- TRANSCEND Leader

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